# FREQUENCY OF ASTHMA IN CHILDREN BORN BY CESAREAN SECTION COMPARED TO THOSE DELIVERED VAGINALLY

By

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## ABSTRACT

**Background:** Cesarean sections (CS) have been reported to increase the risk of asthma in offsprings. This may be due to that infants delivered by CS are unexposed to vaginal flora, according to the 'hygiene hypothesis'

**Objective:** Investigating the risk effects of CS on inducing childhood asthma**.**

**Patients and Methods:** A case-control study was performed on 400 (case = 200, control = 200) children aged 3-12 years referred to outpatient clinics of Al-Hussein University Hospital, the study was conducted from May 2015 to May 2016 . A questionnaire was administered to obtain a demographic, environmental, and clinical history. Sex, mode of delivery, birth weight, age, parental smoking and exclusive breast feeding matching with cases were carried out during sampling for controlling of possible cofounding effects of these factors for asthma**.** Logistic regression models were fitted to compute odds ratios (ORs), and 95% confidence intervals (CI)**.**

**Results:** Risk of being diagnosed with bronchial asthma was significantly higher in children born by Cesarean section (OR=1.8), children in urban areas (OR=1.73), children with history of parental smoking (OR=1.64), low birth weight (OR=2.01) and non exclusive breast feeding (OR=2.12)**.** On performing multiple stepwise logistic regression analysis, CS delivery was the most significant risk factor followed by urban residence followed by non exclusive breast feeding.

**Conclusion**: Birth by cesarean section increased the risk for asthma in childhood

**Keywords:** Asthma, cesarean section, children, vaginal delivery.

## INTRODUCTION

It has been estimated that as many as 300 million people of all ages, suffer from asthma and the burden of this disease to governments, health care systems, families, and patients is increasing worldwide (**Masoli et al., 2014).**

About 334 million people worldwide suffer from asthma; it is the most common chronic disease in children. Asthma is among the top 20 chronic conditions for global ranking of disability-adjusted life years in children (**Asher and Pearce, 2014)** on the other hand cesarean section rates have raised substantially worldwide since the 1980s. In some countries the rate has increased several-fold since 1985 (**Ye et al., 2015)**.

In Egypt the incidence of cesarean delivery has risen significantly. It is

estimated that one of every sex deliveries today in Egypt is being carried out by a cesarean section**,** CS rates in Egypt rose from 4.6% to 51.8% (47.2 points) over the 24 year period **(Betr?n et al., 2016)**.The potential effect of C/S on asthma and allergies is thought to be mediated through immunological mechanisms, mainly focusing on the fact that children born by C/S have reduced exposure to vaginal microbial flora. Differences in the exposure to maternal vaginal or intestinal flora have been shown to be associated with alteration in the neonatal gut microflora **(Sevelsted et al., 2015).**

In CS delivery, the sterile infant is colonized by bacteria from the hospital environment and skin, not by maternal bacteria from the birth canal and perineum. Gut flora has a significant impact on stimulation and maturation of the infant's immune system and its composition varies according to mode of delivery **(Brix et al., 2017).**

## PATIENTS AND METHODS

A case control study was carried out among children 3-12 years of age referred to outpatient clinics of Al-Hussein University Hospital. Since the definitive diagnosis of asthma in children under 3 years is difficult, we did not include these children in the study.

Children who suffered from congenital diseases, those with family history of allergy, and those with any other respiratory co-morbidity like cystic fibrosis; bronchopulmonary dysplasia, and those with any other systemic co-morbidity like hypertension or diabetes were excluded.

**Subjects:** case control study was carried out in Al-Hussein University Hospital from May 2015 to May 2016 on a total of 400 subjects (200 patients with bronchial asthma and 200 subjects as a control group). The asthmatic patients included in the study were those attending allergy and immunology clinic for follow up and taking medication. The control subjects were those accompanying the attendants from other outpatient clinics

**Methodology:** all individuals were subjected to the following steps:

- **Complete history taking:** First, cases were diagnosed by a pediatric pulmonary specialist and if the consent was obtained from children and their parents, a face to face interview was conducted to fill out a questionnaire which consisted of the basic socio-demographic characteristics including: age, sex, residence, parental smoking, birth weight, mode of delivery and breast feeding. This is followed by complete medical history and examination.

- **Investigations:** after taking an informed consent, a chest x ray and a blood sample was collected from each participant and analyzed for serum IgE and complete blood count.

Cross tabulation to visualize distribution of categorical predictors and outcome was done. Factors associated with outcome ≤0.05 were included into the final logistic regression model.

**Statistical analysis:** The data were coded, entered and processed on computer using *SPSS* (version 15). The level $P < 0.05$ was considered the cut-off value for significance.

**Chi-Square test** $X^2$ was used to test the association variables for categorical data.

**Odds Ratio O.R.** compares the odds or the risk that a disease will occur among individuals who have a particular characteristic or who have been exposed to a risk factor to the odds that the disease will occur in individuals who lack the characteristic or have not been exposed

**Student's *t*-test** was used to assess the statistical significance of the difference between two population means in a study involving independent samples.

**Logistic regression**: (multivariate analysis) Logistic regression is useful for situations in which you want to be able to predict the presence or absence of a characteristic or outcome based on values of a set of predictor variables.

## RESULTS

Of 400 children in the study, 200 subjects (50%) were cases of asthma and 200 subjects (50%) were controls. 55.8% of children (n = 223) were male [case group = 54.3% (n = 121), control group = 45.7% (n = 102)] and 44.2% (n = 177) were female [case group = 44.6% (n = 79), control group = 55.4% (n = 98)]. 181 children (45.3%) had been delivered by caesarian section, [case group = 105(58%), control group = 76 (42%)] and 219 children (54.8%) had been delivered by vaginal section, [case group =95(43.4%), control group = 124 (66.6 (Table 1).

In our statistical analysis, there were no significant association between asthma and sex (P =0.056), also no significant association between asthma and sibling order (P=0.8), and no significant association between asthma and consanguinity (P=0.7).

On the other hand a significant association was seen between asthma and younger age, also there were a significant association between asthma and urban residence, delivery by CS, parental smoking, low birth weight and non exclusive breast feeding (P<0.05), (Table 1).

The younger the age of the child, the more likely to have asthma than older age. (OR=0.62, 95%CI=0.55-0.7; P<0.001). Odds of asthma was also higher for urban residence (OR=1.73, 95%CI=1.41-2.61P= 0.010). Children who had delivered by CS had higher odds of asthma (OR=1.8, 95%CI=1.21-2.6; P=0.004), odds of asthma was higher for those children exposed to parental smoking (OR=1.64, 95%CI=1.1-2.46; P=0.015),the probability of occurrence of asthma increased markedly with low birth weight (OR=2.01,95%CI=1.04-3.89;P=0.039),we found children who hadn't exclusively breast-fed for at least 6 month had a higher odds of asthma (OR =2.12,95% CI=1.04-3.2;P<0.001).

On performing multiple analyses, and when the six significant factors entered in multivariate analysis, parental smoking, low birth weight and non exclusive breast feeding became non significant.

On the other hand age, urban residence and CS delivery were the significant risk factors. CS delivery was the most significant risk factor (odds ratio 2.89, 95%CI 1.75-4.78) followed by urban residence (odds ratio 1.7, 95%CI 1.03-2.79) followed by age (odds ratio 0.61, 95% CI .054-0.69). (Table 2)

On performing multiple stepwise logistic regression analysis and when the six significant factors entered in

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multivariate analysis, parental smoking, low birth weight became non significant. CS delivery, urban residence non exclusive breast feeding and age were the significant risk factors.

CS delivery was the most significant risk factor (odds ratio 2.61, 95%CI 1.61-4.23) followed by urban residence (odds ratio 1.76, 95%CI 1.08-2.86) followed by non exclusive breast feeding (odds ratio 1.74, 95% CI 1.08-2.8 Table 2).

**Table (1): The frequency of distribution of case and control groups based various variables in children aged 3-12 years.**

| Groups / Variables | Control (n=200) | Asthmatic (n=200) | P value |
|---|---|---|---|
| **Age** <br> **Range** <br> **Mean ± SD** | (3-12) <br> 6.35±2.57 | (3-12) <br> 3.96±1.93 | **< 0.001** |
| **Sex** <br> **Male** <br> **Female** | 102(51%) <br> 98(49%) | 121(60.5%) <br> 79(39.5%) | 0.056 |
| **Residence** <br> **Rural** <br> **Urban** | 140(70%) <br> 60(30%) | 115(57.5%) <br> 85(42.5%) | **0.009** |
| **Mode of delivery** <br> **VD** <br> **CS** | 124(62%) <br> 76(38%) | 95(47.5%) <br> 105(52.5%) | **0.004** |
| **Sibling order** <br> **1st** <br> **2nd** <br> **3rd** | 76(38%) <br> 66(33%) <br> 58(29%) | 72(36%) <br> 70(35%) <br> 58(29%) | 0.893 |
| **Parental smoking** <br> **No** <br> **Yes** | 129(64.5%) <br> 71(35.5%) | 105(52.5%) <br> 95(47.5%) | **0.015** |
| **Birth weight** <br> **<2500** <br> **>2500** | 15(7.5%) <br> 185(92.5%) | 28(14%) <br> 172(86%) | **0.036** |
| **Consanguinity** <br> **No** <br> **Yes** | 108(54%) <br> 92(46%) | 111(55.5%) <br> 89(44.5%) | 0.763 |
| **Breast feeding** <br> **No** <br> **Yes** | 59(29.5%) <br> 141(70.5%) | 94(47%) <br> 106(53%) | **< 0.001** |

**Table (2): Relationship between asthma and mode of delivery beside various variabilities in logistic regressions**

| Parameters | Simple logistic regression analysis | | Multiple logistic regression analysis | | Multiple stepwise logistic regression analysis | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | AOR (95% CI) | P value | AOR (95% CI) | P value |
| Age | 0.62 (0.55-0.7) | < 0.001 | 0.61 (0.54-0.69) | < 0.001 | 0.6 (0.54-0.68) | < 0.001 |
| Residence (urban) | 1.73 (1.14-2.61) | 0.010 | 1.7 (1.03-2.79) | 0.036 | 1.76 (1.08-2.86) | 0.023 |
| Delivery (CS) | 1.8 (1.21-2.69) | 0.004 | 2.89 (1.75-4.78) | < 0.001 | 2.61 (1.61-4.23) | < 0.001 |
| Parental smoking | 1.64 (1.1-2.46) | 0.015 | 1.45 (0.88-2.38) | 0.148 | | |
| Low birth weight | 2.01 (1.04-3.89) | 0.039 | 1.74 (0.78-3.86) | 0.175 | | |
| No Breast feeding | 2.12 (1.04-3.2) | < 0.001 | 1.49 (0.9-2.47) | 0.119 | 1.74 (1.08-2.8) | 0.023 |

# DISCUSSION

In this case control study we investigated the relationship between modes of delivery and asthma, also we investigated a broad spectrum of environmental factors in the first year of life and asthma in 3-12 years.

According to hygiene hypothesis, which proposes that decreased exposure to environmental agents, including bacteria early in life as a result of modern hygiene practice, shifts immune development towards an allergic phenotype **(Gensollen et al., 2017)**,in our study there was a significantly higher rates of bronchial asthma among cases delivered by CS when compared to those delivered vaginally ,the incidence of bronchial asthma was 58% in children delivered by CS and 43.4% in vaginal delivery. This was in agreement with **Almqvist et al.**

**(2012),** during their register-based cohort study with 87 500 Swedish sibling, found that an increased risk of asthma in the group born by CS.

Indeed, the study by **Kolokotroni et al. (2012)** found that, birth by C/S is associated with asthma and atopic sensitization in childhood. The potential effect of C/S on asthma and allergies is thought to be mediated through immuno-logical mechanisms, mainly focusing on the fact that children born by C/S have reduced exposure to vaginal microbial flora. Differences in the exposure to maternal vaginal or intestinal flora have been shown to be associated with alteration in the neonatal gut microflora and neonatal cytokine response patterns which can subsequently lead to changes in the T helper1/T helper2 cells balance and the risk of developing atopy. A more

likely explanation for the increased prevalence of atopic disease in the cesarean section group could derive from the distinct immunologic effects exerted by the two modes of delivery. Normal vaginal delivery is a stressful process thought to be beneficial for the child's health in promoting lung function and maturation of the immune system. (**Swanson and Robert, 2015**). Distinct effects on breast-feeding also provide notion, as it not only offers optimal nutrition but also supports the proper maturation of gut barrier function through provision of growth factors and immunologically active cells and mediators.

A major regulatory factor in the developing immune system is the gut microflora. Interestingly, differences in intestinal microflora have been found between atopic and nonatopic children (**Abrahamsson et al., 2014**). On the other hand, cesarean section is associated with delayed intestinal colonization,which could deprive the newborn of the immunostimulatory impulses at a very critical period in life when the immune system and the gut barrier maturate. Infants born by vaginal delivery have been shown to have higher nonspecific activity of immune system compared with infants born by cesarean section .Thus cesarean section may be associated with a lack of processes like production of Interleukin 10 (IL-10), which could redirect the constitutive T helper 2 phenotype of the newborn to normal (**Khosravi et al., 2016**).

Interestingly, we found a positive association between secondhand tobaccos smokes exposure and developing asthma, a recent study by **Gonzalez-Barcala et al. (2013)** who found that exposure to environmental tobacco smoke of the childhood population in the community was associated with higher prevalence of asthma .

Another potential risk factor for asthma is low birth weight (**Mu et al., 2014**). This was supported by our finding. Living in urban areas in first year of life is a commonly accepted risk factor for asthma, in our study there was an increase in developing bronchial asthma in children living in urban areas (57.5%) than those living in rural areas (42.5%)[P value =0.009],this is concluded by **Rambabu et al. (2016)** that exposure to outdoor and indoor air pollution remains a significant risk factor for both the development of asthma and the triggering of asthma symptoms, childhood exposure to indoor air pollution, much of which penetrated readily from outdoor sources, may contribute to the development of wheeze symptoms among children ages 5 to 7 years.

We also found exclusive breastfeeding within the first 6 months had higher percentage in control group than in asthma patients. Most of results about breastfeeding and asthma encouraged breastfeeding. There were evidences that breastfeeding is protective for asthma (5-18 years) (**Lumia et al., 2015**). Breastfeeding, especially exclusively breastfeeding, was protective of asthma in

children, (three or more months of exclusive breastfeeding reduced the risk of asthmatic symptoms in the offspring of Latinas **(Bandoli et al., 2015)**.

In our study there was a significantly higher rate of respiratory distress among cases delivered by CS when compared to those delivered vaginally. The incidence of respiratory morbidity was 80% in neonates delivered by CS and 19.8% in normal vaginal delivery infants. This is in agreement with **Levine et al. (2013)** during their computerized retrospective review of 29,669 consecutive deliveries over 7 years to study the relation of mode of delivery and risk of respiratory diseases in the newborn found that those delivered by cesarean section have a fivefold increase in the incidence of respiratory disorders.

In our study, we found a significant decline in asthma symptoms by age. The findings were in agreement with **Andersson et al. ( 2013)** found 20% of a group of individuals who frequently wheezed in childhood to be symptom free at age 19 years.

We suggest that features of childhood asthma such as severity, duration, atopy, bronchial hyperresponsiveness and exposure to smoking can predict the course of asthma into adulthood.

In our study analysis of consanguinity status of the parents of children with asthma and parents among controls indicates that 89/200 (44.5%) of the children with asthma and 92/200 (46%) of the children from controls had positive parental overall consanguinity (P = 0.763). The results of this study suggest that parental consanguinity does not increase the risk of bronchial asthma in children. This is in agreement with **El Mouzan et al. (2014)** who had attempted to evaluate the role of parental consanguinity in the development of bronchial asthma in children. And found that there was no statistically significant risk from parental consanguinity for the development of asthma in children, this in disagreement with **Mahdi et al. (2013)** who examined 200 families and showed that consanguineous marriage and family history of asthma are important determinants in the development of asthma in the offspring.

In our study, 223 male [case group=121, control group=102], and 177 female [case group=79, control group=98], we found no statistically significant differences between males and females in developing bronchial asthma (p value=0.056). **Genuneit (2014)** contradicts this results suggested that gender is an important determinant for asthma and allergies. The impact of gender varies considerably from childhood into adolescence and adulthood. In childhood, boys are consistently found to be at increased risk of asthma, which has been explained by differential growth of lung/airway size, and immunological differences.

In conclusion, birth by cesarean section increases the risk for asthma in childhood as we confirmed a moderate association between CS and bronchial

asthma, consistent with many previous studies. Because asthma constitutes an important and increasing disease burden in children today, and the rate of CS continues to rise, further exploration of the reasons for this association, as well as the possible different effects of planned CS and emergency CS, is important.

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# مدى الإصابة بالربو فى الأطفال الذين يولدون بعملية قيصرية مقارنة مع أولئك المولودين ولادة طبيعية

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**قسم طب الأطفال ـ كلية الطب ـ جامعة الأزهر ـ القاهرة**

**خلفيـة البحـث :** تـؤدى الـولادة عن طريق العمليـة القيصـرية إلـى زيـادة خطـر الإصـابة بـالربو لـدى المواليـد، وربمـا يكـون ذلـك بسـبب أن الـذين يولـدون بعمليـة قيصـرية لا يتعرضـون للبكتريـا النافعـة الموجودة بالغشاء المبطن للمهبل وفقا لنظرية النظافة .

**الهدف من البحث :** تحقيق ما إذا كانت الـولادة بالعمليـة القيصرية تزيد من خطـر الإصـابة بـالربو فى مرحلة الطفولة .

**المرضى وطرق البحث :** أجريت الدراسـة علـى ٤٠٠ طفل (٢٠٠ حالـة مصـابة بـالربو و ٢٠٠ حالـة حاكمة خالية من المرض ) فى أطفال أعمارهم من ٣ إلى ١٢ سنة يترددون علـى العيـادات الخارجية بمستشفى الحسين الجامعى فى الفترة من مـايو ٢٠١٥ إلى مـايو ٢٠١٦ . وقد تـم إستكمال الإستبيان المقدم لكل طفل والذى يتضمن الحصـول علـى التاريخ الديموغرافى والبيئى والسريرى ونوع الجنس وطريقة الـولادة والعمر وتـدخين الوالـدين والرضـاعة الطبيعيـة المطلقة، ومطابقة ذلـك علـى عينـات الأطفال لمعرفة الآثار المحتملة لهذه العوامل فى إحداث مرض الربو .وتم تحليل ذلك بنماذج الإنحدار اللوجيستية لحساب نسب الأرجحية .

**النتائج :** خطر التعرض للإصابة بالربو القصبى أعلى بكثير فى الأطفال الذين يولدون بعملية قيصرية (نسبة الأرجحية ١،٨) ،والأطفال الذين يعيشون فى المناطق الحضرية ( نسبة الأرجحية ١،٧٣) ، والأطفال ناقصى الوزن عند الولادة (نسبة الأرجحية ٢،٠١) ،والأطفال الذين تعرضوا لتدخين أحد الوالـدين (نسبة الأرجحيـة ١،٦٤)، والأطفال الـذين لـم يرضـعوا مـن الثدى رضـاعة مطلقـة (نسبة الأرجحية ٢،١٢) .ومع عمل الإنحدار اللوجيستى التدريجى المتعدد لبيان أى هذه العوامل يحمل معدل أعلى لخطر الإصابة بـالربو وقد تبين أن الـولادة القيصرية أعـلى العوامـل خطـرا (نسبة الأرجحية ٢،٦١) يليه الإقامـة فى المنـاطق الحضرية (نسبة الأرجحيـة ١،٧٦) ،يليه عدم الرضـاعة الطبيعية المطلقة (نسبة الإرجحية ١،٧٤).

**الإستنتاج :** الولادة القيصرية تزيد من خطر الإصابة بالربو فى مرحلة الطفولة .